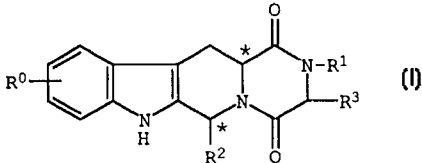
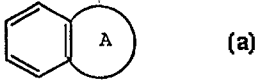


## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b> <b>A61K 31/4985, A61P 9/08, 15/10</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 00/15228</b> <b>(43) International Publication Date:</b> 23 March 2000 (23.03.00)
<b>(21) International Application Number:</b> PCT/US99/19466 <b>(22) International Filing Date:</b> 26 August 1999 (26.08.99) <b>(30) Priority Data:</b> 09/154,051 16 September 1998 (16.09.98) US <b>(71) Applicant:</b> ICOS CORPORATION [US/US]; 22021 20th Avenue S.E., Bothell, WA 98021 (US). <b>(72) Inventors:</b> DAUGAN, Alain, Claude-Marie; 100, route de Versailles, F-78163 Marly Le Roi Cedex (FR). GELLIBERT, Françoise; 100, route de Versailles, F-78163 Marly Le Roi Cedex (FR). <b>(74) Agent:</b> NAPOLI, James, J.; Marshall, O'Toole, Gerstein, Murray & Borun, 6300 Sears Tower, 233 South Wacker Drive, Chicago, IL 60606 (US).		<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> COMBINATIONS OF TETRACYCLIC CYCLIC GMP-SPECIFIC PHOSPHODIESTERASE INHIBITORS WITH FURTHER THERAPEUTIC AGENTS  <div style="display: flex; justify-content: space-around; align-items: center;"> <div data-bbox="354 1199 773 1360">  <p style="text-align: center;">(I)</p> </div> <div data-bbox="938 1230 1192 1310">  <p style="text-align: center;">(a)</p> </div> </div> <b>(57) Abstract</b>  <p>A compound of formula (I) and salts and solvates thereof, in which: R<sup>0</sup> represents hydrogen, halogen, or C<sub>1-6</sub>alkyl; R<sup>1</sup> represents hydrogen, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, haloC<sub>1-6</sub>alkyl, C<sub>3-8</sub>cycloalkyl, C<sub>3-8</sub>cyloalkylC<sub>1-3</sub>alkyl, arylC<sub>1-3</sub>alkyl, or heteroarylC<sub>1-3</sub>alkyl; R<sup>2</sup> represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan, and pyridine, or an optionally substituted bicyclic ring (a) attached to the rest of the molecule via one of the benzene ring carbon atoms, and wherein the fused ring (A) is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated, and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur, and nitrogen; and R<sup>3</sup> represents hydrogen or C<sub>1-3</sub>alkyl, or R<sup>1</sup> and R<sup>3</sup> together represent a 3- or 4-membered alkyl or alkenyl chain. A compound of formula (I) is a potent and selective inhibitor of cyclic guanosine 3', 5'-monophosphate specific phosphodiesterase (cGMP specific PDE) having a utility in a variety of therapeutic areas where such inhibition is beneficial, including the treatment of cardiovascular disorders and erectile dysfunction.</p>		

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**COMBINATIONS OF TETRACYCLIC CYCLIC GMP-SPECIFIC PHOSPHODIESTERASE  
INHIBITORS WITH FURTHER THERAPEUTIC AGENTS**

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**FIELD AND BACKGROUND OF THE INVENTION**

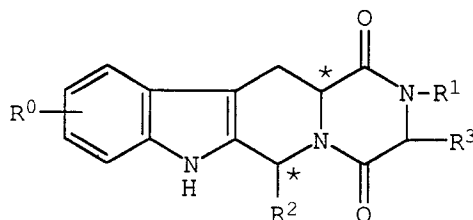
10 This invention relates to a series of  
tetracyclic derivatives, to processes for their  
preparation, pharmaceutical compositions containing  
them, and to their use as therapeutic agents. In  
particular, the invention relates to tetracyclic  
15 derivatives that are potent and selective inhibitors  
of cyclic guanosine 3',5'-monophosphate specific  
phosphodiesterase (cGMP-specific PDE) having utility  
in a variety of therapeutic areas where such inhibi-  
tion is thought to be beneficial, including the  
treatment of cardiovascular disorders and erectile  
dysfunction.

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**SUMMARY OF THE INVENTION**

Thus, according to a first aspect, the  
present invention provides compounds of formula (I)

25



(I)

- 2 -

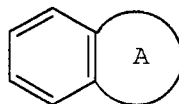
and salts and solvates (e.g., hydrates) thereof, in which:

$R^0$  represents hydrogen, halogen, or  $C_{1-6}$ alkyl;

5  $R^1$  represents hydrogen,  $C_{1-6}$ alkyl,  $C_{2-6}$ -alkenyl,  $C_{2-6}$ alkynyl, halo $C_{1-6}$ alkyl,  $C_{3-8}$ cycloalkyl,  $C_{3-8}$ cycloalkyl $C_{1-3}$ alkyl, aryl $C_{1-3}$ alkyl, or hetero-aryl $C_{1-3}$ alkyl;

10  $R^2$  represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan, and pyridine, or an optionally substituted bicyclic ring

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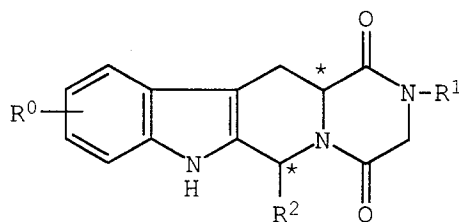


attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring  
20 A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur, and nitrogen; and

25  $R^3$  represents hydrogen of  $C_{1-3}$ alkyl, or  $R^1$  and  $R^3$  together represent a 3- or 4-membered alkyl or alkenyl chain.

There is further provided by the present invention a subgroup of compounds for formula (I), the subgroup comprising compounds of formula (Ia)

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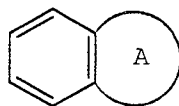
(Ia)

and salts and solvates (e.g., hydrates) thereof, in which:

$R^0$  represents hydrogen, halogen, or  $C_{1-6}$ alkyl;

$R^1$  represents hydrogen,  $C_{1-6}$ alkyl, halo $C_{1-6}$ alkyl,  $C_{3-8}$ cycloalkyl $C_{1-3}$ alkyl, aryl $C_{1-3}$ alkyl, or heteroaryl $C_{1-3}$ alkyl; and

$R^2$  represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan, and pyridine, or an optionally substituted bicyclic ring

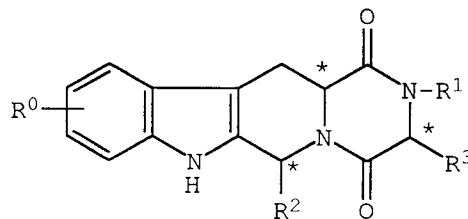


attached to the rest of the molecule via one of the benzene ring carbon atoms, and wherein the fused ring A is a 5- or 6-membered ring which can be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur, and nitrogen.

There is yet further provided by the present invention a further subgroup of compounds of

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formula (I), the compounds comprising compounds of  
formula (Ib)



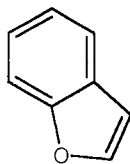
(Ib)

and solvates (e.g., hydrates) thereof, in which:

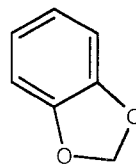
$R^0$  represents hydrogen, halogen, or  $C_{1-6}$ -alkyl;

$R^1$  represents hydrogen or  $C_{1-6}$ alkyl;

$R^2$  represents the bicyclic ring



or



which can be optionally substituted by one or more  
groups selected from halogen and  $C_{1-3}$ alkyl; and

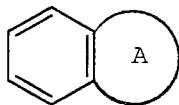
$R^3$  represents hydrogen or  $C_{1-3}$ alkyl.

Within  $R^1$  above, the term "aryl" as part of  
an aryl $C_{1-3}$ alkyl group means phenyl or phenyl substi-  
tuted by one or more (e.g., 1, 2, or 3) substituents  
selected from halogen,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy, and  
methylenedioxy. The term "heteroaryl" as part of a  
heteroaryl $C_{1-3}$ alkyl group means thienyl, furyl, or  
pyridyl, each optionally substituted by one or more  
(e.g., 1, 2, or 3) substituents selected from halo-

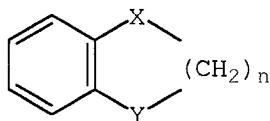
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gen, C<sub>1-6</sub>alkyl, and C<sub>1-6</sub>alkoxy. The term "C<sub>3-8</sub>cycloalkyl" as a group or part of a C<sub>3-8</sub>cycloalkylC<sub>1-3</sub>alkyl group means a monocyclic ring comprising three to eight carbon atoms. Examples of suitable cycloalkyl rings include the C<sub>3-6</sub>cycloalkyl rings cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

Within R<sup>2</sup> above, optional benzene ring substituents are selected from one or more (e.g., 1, 2, or 3) atoms or groups comprising halogen, hydroxy, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, CO<sub>2</sub>R<sup>b</sup>, haloC<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkoxy, cyano, nitro, and NR<sup>a</sup>R<sup>b</sup>, where R<sup>a</sup> and R<sup>b</sup> are each hydrogen or C<sub>1-6</sub>alkyl, or R<sup>a</sup> also can represent C<sub>2-7</sub>alkanoyl or C<sub>1-6</sub>alkylsulphonyl. Optional substituents for the remaining ring systems are selected from one or more (e.g., 1, 2, or 3) atoms or groups comprising halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, and arylC<sub>1-3</sub>alkyl as defined above. The bicyclic ring



can, for example, represent naphthalene, a heterocycle such as benzoxazole, benzothiazole, benzisoxazole, benzimidazole, quinoline, indole, benzothiophene, benzofuran, or



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wherein n is an integer 1 or 2 and X and Y each can represent CH<sub>2</sub>, O, S, or NH.

In the above definitions, the term "alkyl," as a group or part of a group, means a  
5 straight chain or, where available, a branched chain moiety containing the indicated number of carbon atoms. For example, it can represent a C<sub>1-4</sub>alkyl function as represented by methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, and t-butyl. The term  
10 "alkenyl" as used herein includes straight chained and branched alkenyl groups containing the indicated number of carbon atoms, such as vinyl and allyl groups. The term "alkynyl" as used herein includes straight chained and branched alkynyl groups con-  
15 taining the indicated number of carbon atoms, suitably acetylene.

The term "halogen" herein means a fluorine, chlorine, bromine, or iodine atom.

The term "haloC<sub>1-6</sub>alkyl" means an alkyl  
20 group as defined above comprising one to six carbon atoms substituted at one or more carbon atoms by one or more (e.g., 1, 2, or 3) halogen atoms. Similarly, a haloC<sub>1-6</sub>alkoxy group is a haloC<sub>1-6</sub>alkyl group as defined above linked to the R<sup>2</sup> benzene ring via an  
25 oxygen atom. Examples of haloC<sub>1-6</sub>alkyl groups include trifluoromethyl and 2,2,2-trifluoroethyl. An example of a haloC<sub>1-6</sub>alkoxy group is trifluoromethoxy. The term "C<sub>2-7</sub>alkanoyl" means a C<sub>1-6</sub>alkanoyl group where the C<sub>1-6</sub>alkyl portion is as defined  
30 above. An example of a suitable C<sub>2-7</sub>alkanoyl group is the C<sub>2</sub>alkanoyl group acetyl.

When R<sup>0</sup> is a halogen atom or a C<sub>1-6</sub>alkyl group, this substituent can be sited at any avail-



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able position on the phenyl portion of the tetra-cyclic ring. However, a particular site of attachment is the ring 10-position.

5       The compounds of formula (I) can contain  
two or more asymmetric centers, and, thus, can exist  
as enantiomers or diastereoisomers. In particular,  
in formula (I) above, two ring chiral centers are  
denoted with asterisks. It is to be understood that  
the invention includes both mixture and separate  
10   individual isomers of the compounds of formula (I).

      The compounds of formula (I) also can  
exist in tautomeric forms, and the invention  
includes both mixtures and separate individual  
tautomers thereof.

15       The pharmaceutically acceptable salts of  
the compounds of formula (I) which contain a basic  
center are acid addition salts formed with pharma-  
ceutically acceptable acids. Examples include the  
hydrochloride, hydrobromide, sulfate or bisulfate,  
20   phosphate or hydrogen phosphate, acetate, benzoate,  
succinate, fumarate, maleate, lactate, citrate,  
tartrate, gluconate, methanesulphonate, and p-  
toluenesulphonate salts. Compounds of formula (I)  
also can provide pharmaceutically acceptable metal  
25   salts, in particular alkali metal salts, with bases.  
Examples include the sodium and potassium salts.

      A particular group of compounds of the  
invention are those compounds of formula (I) in  
which  $R^0$  is hydrogen or halogen (e.g., fluorine),  
30   especially hydrogen.

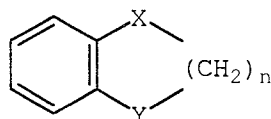
      Another particular group of compounds of  
the invention are those compounds of formula (I) in  
which  $R^1$  represents hydrogen,  $C_{1-4}$ alkyl, halo $C_{1-4}$ alkyl,

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C<sub>3-6</sub>cycloalkyl, C<sub>3-6</sub>cycloalkylmethyl, pyridylC<sub>1-3</sub>alkyl, furylC<sub>1-3</sub>alkyl, or optionally substituted benzyl.

Within this particular group of compounds, examples of C<sub>1-4</sub>alkyl groups are methyl, ethyl, n-propyl, i-propyl, and n-butyl. Examples of C<sub>3-6</sub>cycloalkylmethyl groups are cyclopropylmethyl and cyclohexylmethyl. Examples of optionally substituted, benzyl groups include benzyl and halobenzyl (e.g., fluorobenzyl).

A further group of compounds of the invention are those compounds of formula (I) in which R<sup>2</sup> represents an optionally substituted benzene, thiophene, furan, pyridine, or naphthalene ring, or an optionally substituted bicyclic ring



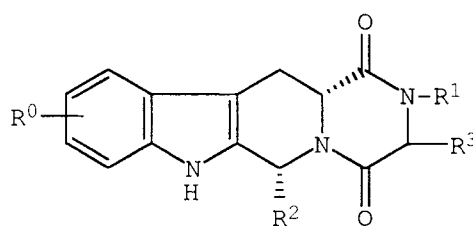
wherein n is 1 or 2, and X and Y are each CH<sub>2</sub> or O. Within this particular group of compounds, examples of substituted benzene groups are benzene substituted by one of halogen (e.g., chlorine), hydroxy, C<sub>1-3</sub>alkyl (e.g., methyl, ethyl, or i-propyl), C<sub>1-3</sub>alkoxy (e.g., methoxy or ethoxy), CO<sub>2</sub>R<sup>b</sup>, halomethyl (e.g., trifluoromethyl), halomethoxy (e.g., trifluoromethoxy), cyano, nitro, or NR<sup>a</sup>R<sup>b</sup> wherein R<sup>a</sup> and R<sup>b</sup> are each hydrogen or methyl, or R<sup>a</sup> is acetyl, or benzene substituted by dihalo (e.g., dichloro) or by C<sub>1-3</sub>alkoxy (e.g., methoxy) and one of halogen (e.g., chlorine) and hydroxy. An example of a substituted

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thiophene ring is a halo (e.g., bromo) substituted thiophene ring.

A still further particular group of compounds of formula (I) are those where  $R^3$  represents hydrogen or  $R^1$  and  $R^3$  together represent a 3-membered alkyl chain.

A preferred group of compounds of the invention are the cis isomers of formula (I) represented by formula (Ic)



(Ic)

and mixtures thereof with their cis optical enantiomers, including racemic mixtures, and salts and solvates (e.g., hydrates) of these compounds in which  $R^0$  is hydrogen or halogen (e.g., fluorine), especially hydrogen, and  $R^1$ ,  $R^2$ , and  $R^3$  are as defined previously.

The single isomers represented by formula (Ic), i.e., the 6R, 12aR isomers, are particularly preferred.

Within the above definitions,  $R^1$  preferably can represent  $C_{1-4}$ alkyl (e.g., methyl, ethyl, i-propyl, and n-butyl),  $C_{3-6}$ cycloalkyl (e.g., cyclopentyl) or  $C_{3-6}$ cycloalkylmethyl (e.g., cyclopropylmethyl).

$R^2$  preferably can represent a substituted benzene ring such as benzene substituted by  $C_{1-3}$ -

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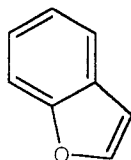
alkoxy (e.g., methoxy) or by C<sub>1-3</sub>alkoxy (e.g., methoxy) and halogen (e.g., chlorine), particularly 4-methoxyphenyl or 3-chloro-4-methoxyphenyl, or R<sup>2</sup> preferably can represent 3,4-methylenedioxyphenyl.

5 A particularly preferred subgroup of compounds according to the present invention are compounds wherein R<sup>0</sup> represents hydrogen.

A further preferred subgroup includes compounds wherein R<sup>1</sup> is selected from hydrogen,  
10 methyl, and isopropyl.

Preferably, R<sup>2</sup> represents the unsubstituted bicyclic ring

15



20

A still further subgroup of compounds of formula (I), are compounds wherein R<sup>3</sup> represents hydrogen or methyl.

25 It is to be understood that the present invention covers all appropriate combinations of particular and preferred groupings hereinabove.

Particular individual compounds of the invention include:

30 cis-2,3,6,7,12,12a-hexahydro-2-(4-pyridyl-methyl)-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

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cis-2,3,6,7,12,12a-hexahydro-6-(2,3-dihydrobenzo[b]furan-5-yl)-2-methyl-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

5 cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-methylpyrazino[2',1':6,1]pyrido[3,4-b]-indole-1,4-dione;

cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]-indole-1,4-dione;

10 (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-isopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-cyclopentyl-6-(3,4-methylenedioxyphenyl)-pyrazino-  
15 [2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-cyclopropylmethyl-6-(4-methoxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(3-chloro-4-methoxyphenyl)-2-methyl-pyrazino[2',1':-  
20 6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

25 (6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(5aR, 12R, 14aS)-1,2,3,5,6,11,12,14a-octahydro-12-(3,4-methylenedioxyphenyl)-pyrrolo-  
30 [1",2":4'5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-5-1,4-dione;

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(6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(5-benzofuranyl)-2-methyl-pyrazino[2',1':6,1]pyrido-[3,4-b]indole-1,4-dione;

5 (6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(5-benzofuranyl)-pyrazino[2',1':6,1]pyrido[3,4-b]-indole-1,4-dione; —

(3S, 6R, 12aR)-2,3,6,7,12,12a-hexahydro-6-(5-benzofuranyl)-3-methyl-pyrazino[2',1':6,1]pyrido-[3,4-b]indole-1,4-dione;

10 (3S, 6R, 12aR)-2,3,6,7,12,12a-hexahydro-6-(5-benzofuranyl)-2,3-dimethyl-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione;

(6R, 12aR)-2,3,6,7,12,12a-hexahydro-6-(5-benzofuranyl)-2-isopropyl-pyrazino[2',1':6,1]pyrido-  
15 [3,4-b]indole-1,4-dione; and physiologically acceptable solvates (e.g., hydrates) thereof.

Specific compounds of the invention are:

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino-  
20 [2',1':6,1]pyrido[3,4-b]indole-1,4-dione; and

(6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(5-benzofuranyl)-2-methyl-pyrazino[2',1':6,1]pyrido-[3,4-b]indole-1,4-dione; and physiologically acceptable solvates (e.g., hydrates) thereof.

25

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

It has been shown that compounds of the present invention are potent and selective inhibitors of cGMP-specific PDEs 1, 5, and 6, and particularly PDE5. Thus, compounds of formula (I) are  
30 of interest for use in therapy, specifically for the

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treatment of a variety of conditions where selective inhibition of PDE5 is considered to be beneficial.

In summary, the biochemical, physiological, and clinical effects of PDE5 inhibitors suggest their utility in a variety of disease states in which modulation of smooth muscle, renal, hemostatic, inflammatory, and/or endocrine function is desirable. The compounds of formula (I), therefore, have utility in the treatment of a number of disorders, including stable, unstable, and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, acute respiratory distress syndrome, acute and chronic renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g., postpercutaneous transluminal coronary or carotid angioplasty, or post-bypass surgery graft stenosis), peripheral vascular disease, vascular disorders, such as Raynaud's disease, thrombocytopenia, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, osteoporosis, preterm labor, benign prostatic hypertrophy, male and female erectile dysfunction, and diseases characterized by disorders of gut motility (e.g., irritable bowel syndrome).

An especially important use is the treatment of male erectile dysfunction, which is one form of impotence and is a common medical problem. Impotence can be defined as a lack of power, in the male, to copulate and can involve an inability to achieve penile erection or ejaculation, or both. The incidence of erectile dysfunction increases with age, with about 50% of men over the age of 40 suffering from some degree of erectile dysfunction.

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Many compounds have been investigated for their therapeutic potential in the treatment of MED, including phenoxybenzamine, papaverine, prostaglandin E1 (PGE1), and phentolamine. These compounds, either alone or in combination, are typically self-administered by intracavernosal (i.c.) injection. While such treatments are effective, a treatment that is less invasive than injection therapy is preferred because pain, priapism, and fibrosis of the penis are associated with the i.c. administration of these agents.

For example, alprostadil (i.e., prostaglandin E1) delivered by intraurethral deposition has been approved for the treatment of MED. However, clinical studies showed that this route of administration is not effective in all patients. In addition, phentolamine and apomorphine are being evaluated as oral and sublingual therapies for MED, but neither compound has demonstrated efficacy across a broad range of subjects. Potassium channel openers (KCO) and vasoactive intestinal polypeptide (VIP) also have been shown to be active i.c., but cost and stability issues could limit development of the latter. An alternative to the i.c. route is the use of glyceryl trinitrate (GTN) patches applied to the penis, which has been shown to be effective but produces side effects in both patient and partner.

As an alternative to pharmacological treatment, a variety of penile prostheses have been used to assist achievement of an erection. The short-term success rate is good, but problems with infection and ischemia, especially in diabetic men,



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make this type of treatment a final option rather than a first-line therapy.

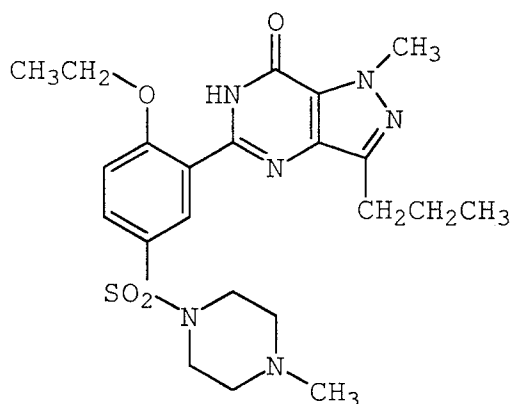
Because of the disadvantages of prior treatments for MED, new strategies to improve  
5     erectile response that exploit different physiologi-  
cal mechanisms are being investigated. One area of investigation is increasing the intracellular concentration of cGMP by providing a new type of oral therapy for the treatment of MED.

10             Increasing cGMP concentration is an important step in the physiology of penile erections. A penile erection is caused by neural stimuli that ultimately cause vasodilation of the arteries and sinusoidal spaces of the corpus  
15     cavernosum. Research indicates that nitric oxide plays a central role in this vasodilation.

              In particular, atrial natriuretic peptides (ANP) and nitric oxide (NO, sometimes referred to as endothelium-derived relaxing factor or EDRF) relax  
20     smooth muscle by increasing guanylyl cyclase activity, which raises intracellular cGMP concentration. Intracellular cGMP is hydrolyzed by phosphodiesterases (PDEs), thereby terminating the action of the cyclic nucleotide. PDE5 is the major  
25     cGMP hydrolyzing enzyme in vascular smooth muscle. Accordingly, PDE5 inhibition potentiates the relaxant effects of ANP and nitric oxide by increasing the cGMP levels. Therefore, a compound that inhibits the PDE5 enzyme (and thereby indirectly  
30     inhibits the hydrolysis of cGMP) should potentiate the vascular response to nitric oxide, thereby facilitating the achievement and maintenance of erection.

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PDE5 inhibitors have potential for use in treating male erectile dysfunction (MED), hypertension, heart failure, and other disease states because of their ability to facilitate the action of ANP and NO. For example, sildenafil, a PDE inhibitor showing little selectivity with respect to PDE6, has the structure:



and has shown efficacy in oral administration clinical trials for MED, which supports the hypothesis that augmenting normal or subnormal guanylyl cyclase stimuli has therapeutic benefits.

It is envisioned, therefore, that compounds of formula (I) are useful in the treatment of erectile dysfunction. Furthermore, the compounds can be administered orally, thereby obviating the disadvantages associated with intracavernosal administration. Thus, the present invention concerns the use of compounds of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manu-

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fracture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

5 It also has been observed that human corpus cavernosum contains three distinct PDE enzymes (see A. Taher et al., *J. Urol.*, 149, p. 285A (1993)), one of which is the cGMP-specific PDE5. As a consequence of the selective PDE5 inhibition exhibited by compounds of the present invention, the  
10 present compounds sustain cGMP levels, which in turn mediate relaxation of the corpus cavernosum tissue and consequent penile erection.

Although the compounds of the invention are envisioned primarily for the treatment of  
15 erectile dysfunction in humans, such as male erectile dysfunction and female sexual dysfunction, including orgasmic dysfunction related to clitoral disturbances, they also can be used for the treatment of premature labor and dysmenorrhea.

20 It is understood that references herein to treatment extend to prophylaxis, as well as treatment of established conditions.

It also is understood that "a compound of formula (I)," or a physiologically acceptable salt  
25 or solvate thereof, can be administered as the neat compound, or as a pharmaceutical composition containing either entity.

A further aspect of the present invention is providing a compound of formula (I) for use in  
30 the treatment of stable, unstable, and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, congestive heart failure, acute respiratory distress

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syndrome, acute and chronic renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g., post-PTCA or post-bypass graft stenosis), peripheral vascular disease, vascular disorders such as Raynaud's disease, thrombo-  
5 cythemia, inflammatory diseases, prophylaxis of myocardial infarction, prophylaxis of stroke, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, osteoporosis, preterm  
10 labor, benign prostatic hypertrophy, male and female erectile dysfunction, or diseases characterized by disorders of gut motility (e.g., IBS).

According to another aspect of the present invention, there is provided the use of a compound  
15 of formula (I) for the manufacture of a medicament for the treatment of the above-noted conditions and disorders.

In a further aspect, the present invention provides a method of treating the above-noted conditions and disorders in a human or nonhuman animal  
20 body which comprises administering to said body a therapeutically effective amount of a compound of formula (I).

Compounds of the invention can be administered by any suitable route, for example by oral,  
25 buccal, inhalation, sublingual, rectal, vaginal, transurethral, nasal, topical, percutaneous, i.e., transdermal, or parenteral (including intravenous, intramuscular, subcutaneous, and intracoronary)  
30 administration. Parenteral administration can be accomplished using a needle and syringe, or using a high pressure technique, like POWDERJECT™. Oral administration generally is preferred.

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With respect to treating sexual dysfunction and particularly erectile dysfunction in humans, oral administration of the compounds of the invention is the preferred route. Oral administration is the most convenient and avoids the disadvantages associated with intracavernosal administration. For patients suffering from a swallowing disorder or from impairment of drug absorption after oral administration, the drug can be administered parenterally, e.g., sublingually or buccally.

For administration to man in the curative or prophylactic treatment of the conditions and disorders identified above, oral dosages of a compound of formula (I) generally are about 0.5 to about 1000 mg daily for an average adult patient (70 kg). Thus, for a typical adult patient, individual tablets or capsules contain 0.2 to 500 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day. Dosages for intravenous, buccal, or sublingual administration typically are 0.1 to 500 mg per single dose as required. In practice, the physician determines the actual dosing regimen which is most suitable for an individual patient, and the dosage varies with the age, weight, and response of the particular patient. The above dosages are exemplary of the average case, but there can be individual instances in which higher or lower dosages are merited, and such are within the scope of this invention.

For human use, a compound of the formula (I) can be administered alone, but generally is

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administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, the compound can be administered orally, buccally, or sublingually in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules, either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. Such liquid preparations can be prepared with pharmaceutically acceptable additives, such as suspending agents (e.g., methylcellulose, a semisynthetic glyceride such as witepsol, or mixtures of glycerides such as a mixture of apricot kernel oil and PEG-6 esters, or mixtures of PEG-8 and caprylic/capric glycerides). A compound also can be injected parenterally, for example, intravenously, intramuscularly, subcutaneously, or intracoronarily. For parenteral administration, the compound is best used in the form of a sterile aqueous solution which can contain other substances, for example, salts, or monosaccharides, such as mannitol or glucose, to make the solution isotonic with blood.

For veterinary use, a compound of formula (I) or a nontoxic salt thereof, is administered as a suitably acceptable formulation in accordance with normal veterinary practice. The veterinarian can readily determine the dosing regimen and route of administration that is most appropriate for a particular animal.

Thus, the invention provides in a further aspect a pharmaceutical composition comprising a

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compound of the formula (I), together with a pharmaceutically acceptable diluent or carrier therefor.

There is further provided by the present invention a process of preparing a pharmaceutical composition comprising a compound of formula (I),  
5 which process comprises mixing a compound of formula (I), together with a pharmaceutically acceptable diluent or carrier therefor.

In a particular embodiment, the invention  
10 includes a pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, together with a pharmaceutically  
15 acceptable diluent or carrier.

A compound of formula (I) also can be used in combination with other therapeutic agents which can be useful in the treatment of the above-mentioned and other disease states. The invention  
20 thus provides, in another aspect, a combination of a compound of formula (I), together with a second therapeutically active agent.

A compound of formula (I) can be used in the preparation of a medicament for co-administration with the second therapeutically active agent in  
25 treatment of conditions where inhibition of a cGMP-specific PDE is beneficial. In addition, a compound of formula (I) can be used in the preparation of a medicament for use as adjunctive therapy with a  
30 second therapeutically active compound to treat such conditions. Appropriate doses of known second therapeutic agents for use in combination with a

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compound of formula (I) are readily appreciated by those skilled in the art.

In particular, because compounds of the present invention maintain cGMP levels, the compounds of formula (I) can provide beneficial anti-platelet, antineutrophil, antivasospastic, vasodilatory, natriuretic, and diuretic activities, as well as potentiate the effects of endothelium-derived relaxing factor (EDRF), gastric NO administration, nitrovasodilators, atrial natriuretic factor (ANF), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), and endothelium-dependent relaxing agents such as bradykinin, acetylcholine, and 5-HT<sub>1</sub>.

The present selective PDE5 inhibitors in combination with vasodilators, including nitric oxide and nitric oxide donators and precursors, such as the organic nitrate vasodilators which act by releasing nitric oxide *in vivo*, are especially useful in treatment of angina, congestive heart failure, and malignant hypertension (e.g., pheochromocytoma). Related to the capacity of the present PDE5 inhibitors to potentiate nitric oxide donors and precursors is their ability, in spontaneously hypertensive rats, to reverse the desensitization to these agents that occurs with chronic use.

Examples of vasodilators that can be used in conjunction with the compounds of formula (I) include, but are not limited to, (a) organic nitrates, such as nitroglycerin, isosorbide dinitrate, pentaerythrityl tetranitrate, isosorbide-5-mononitrate, propatyl nitrate, trolnitrate, nicroandil, mannitol hexanitrate, inositol hexanitrate, N-[3-nitratopivaloyl]-L-cysteine ethyl ester, (b)



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organic nitrites, like isoamyl nitrite, (c) thio-nitrites, (d) thionitrates, (e) S-nitrosothiols, like S-nitroso-N-acetyl-D,L-penicillamine, (f) nitrosoproteins, (g) substituted furoxanes, such as  
5 1,2,5-oxadiazole-2-oxide and furazan-N-oxide, (h) — substituted sydnonimines, such as molsidomine and mesocarb, (i) nitrosyl complex compounds, like iron nitrosyl compounds, especially sodium nitroprusside, and (j) nitric oxide (NO) itself.

10 Other classes of therapeutic agents that can be used in conjunction with the compounds of formula (I), in addition to vasodilators, include, but are not limited to,  $\alpha$ -adrenergic blockers, mixed  $\alpha,\beta$ -blockers, prostaglandin EI (PGEI) and prosta-  
15 cyclin (PGI2), angiotensin converting enzyme inhibitors (ACE inhibitors), neutral endopeptidase (NEP) inhibitors, centrally acting dopaminergic agents (such as apomorphine), vasoactive intestinal peptides (VIP), calcium channel blockers, and compounds  
20 like thiazides.

Alpha-adrenergic blockers inhibit vasoconstriction in the corpus cavernosum. Because PDE5 inhibitors enhance vasodilation of the same smooth muscle tissue, a PDE5 inhibitor of formula (I) and  
25 an  $\alpha$ -adrenergic blocker, like phentolamine or prazosin, or a centrally acting dopaminergic agent, like apomorphine, can be expected to potentiate one another in a treatment for MED or other disorders. Potentiation of mixed  $\alpha,\beta$ -blockers, like carvedilol,  
30 which is employed in treatment of hypertension, also is expected. Similarly,  $\alpha_2$ -adrenergic blockers, like yohimbine, can be potentiated.

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Prostaglandin E1 enhances relaxation of the corpus cavernosum by increasing the formation of cyclic AMP. Cyclic AMP can be degraded in the corpus cavernosum by PDE3, which is inhibited by cyclic GMP. By maintaining cyclic GMP levels, a PDE5 inhibitor can indirectly inhibit PDE3 activity, and hence block degradation of cyclic AMP. Therefore, a PDE5 inhibitor of formula (I) can be expected to potentiate the activity of PGE1 in the treatment of MED or compounds having similar activities, such as PGI2, in the treatment of pulmonary hypertension, for example.

Angiotensin converting enzyme (ACE) inhibitors block the conversion of angiotensin I into angiotensin II, which causes systemic vasoconstriction and the retention of sodium and water. PDE5 inhibitors cause vasodilation in hypertensive animals, and stimulate the excretion of sodium and water in normotensive animals. Therefore, a PDE5 inhibitor of formula (I) can be combined with an ACE inhibitor to achieve more powerful vasodilatory and natriuretic effects in, for example, treatment of congestive heart failure or hypertensive states.

Neutral endopeptidase (NEP) inhibitors inhibit the degradation of atrial natriuretic peptide (ANP) by NEP. PDE5 inhibitors can be expected to potentiate the action of ANP by inhibiting degradation of its second messenger, cyclic GMP, and, therefore, a compound of formula (I) can potentiate the effects of agents, like NEP inhibitors, that increase blood levels of ANP.

The combination referred to above can be presented for use in the form of a single pharma-

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ceutical formulation, and, thus, pharmaceutical compositions comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier comprise a further aspect of the invention.

The individual components of such a combination, therefore, can be administered either sequentially or simultaneously from the same or separate pharmaceutical formulations. As is the case for the PDE5 inhibitors of formula (I), a second therapeutic agent can be administered by any suitable route, for example, by oral, buccal, inhalation, sublingual, rectal, vaginal, trans-urethral, nasal, topical, percutaneous (i.e., transdermal), or parenteral (including intravenous, intramuscular, subcutaneous, and intracoronary) administration.

In some embodiments, the compound of formula (I) and the second therapeutic agent are administered by the same route, either from the same or from different pharmaceutical compositions. However, in other embodiments, using the same route of administration for the compound of formula (I) and the second therapeutic agent either is impossible or is not preferred. For example, if the second therapeutic agent is nitric oxide, which typically is administered by inhalation, the compound of formula (I) must be administered by a different route. Furthermore, if a compound of formula (I) is used in combination with a nitrate vasodilator, for example, in treatment of an erectile dysfunction, it is preferred that the compound of formula (I) is administered orally and

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the vasodilator is administered topically, and preferably in a manner which avoids substantial systemic delivery of the nitrate.

5           The combination of a compound of formula (I) and a second therapeutic agent is envisioned in the treatment of several disease states. Examples of such treatments are the systemic and topical treatment of male and female sexual dysfunction, wherein a compound of formula (I) is used in combination with phentolamine, prazosin, apomorphine, PDE1, or a vasoactive intestinal peptide. The compound of formula (I) can be administered orally or transurethally, and the second therapeutic agent can be administered orally, topically, or 10 intracavernosally, for example. Persons skilled in the art are aware of the best modes of administration for each therapeutic agent, either alone or in a combination.

Other disease states that can be treated by a combination of a compound of formula (I) and a second therapeutic agent include, but are not limited to:

- 25           (a) treatment of hypertension using a compound of formula (I) in combination with an  $\alpha$ -adrenergic blocker, a mixed  $\alpha,\beta$ -blocker, like carvedilol, a thiazide, sodium nitroprusside, an ACE inhibitor, or a calcium channel blocker;
- 30           (b) treatment of pulmonary hypertension using a compound of formula (I) in combination with inhaled NO or other

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inhaled vasodilators, or with PGI2 administered via an IV pump; and

- (c) treatment of chronic obstructive pulmonary disease using a compound of formula (I) in combination with inhaled NO.

Examples of individual compounds of the invention for use in the treatment of erectile dysfunction include:

cis-2,3,6,7,12,12a-hexahydro-2-(4-pyridyl-methyl)-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

cis-2,3,6,7,12,12a-hexahydro-6-(2,3-dihydrobenzo[b]furan-5-yl)-2-methyl-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

cis-2,3,6,7,12,12a-hexahydro-2-butyl-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]-indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-isopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-cyclopentyl-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-cyclopropylmethyl-6-(4-methoxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(3-chloro-4-methoxyphenyl)-2-methyl-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

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(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

5 (6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(5aR, 12R, 14aS)-1,2,3,5,6,11,12,14a-octahydro-12-(3,4-methylenedioxyphenyl)-pyrrolo-[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-10 5-1,4-dione;

cis-2,3,6,7,12,12a-hexahydro-2-cyclopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(3S, 6R, 12aR)-2,3,6,7,12,12a-hexahydro-3-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino-15 [2',1':6,1]pyrido[3,4-b]indole-1,4-dione; and physiologically acceptable salts and solvates (e.g., hydrates) thereof.

Especially useful specific compounds of the invention are:

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione; and

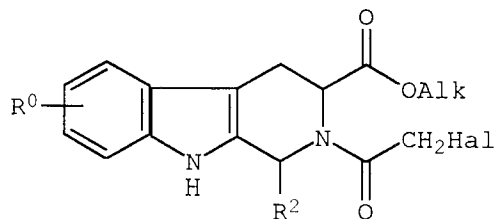
(3S, 6R, 12aR)-2,3,6,7,12,12a-hexahydro-25 2,3-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione; and physiologically acceptable salts and solvates (e.g., hydrates) thereof.

Compounds of formula (I) can be prepared 30 by any suitable method known in the art or by the following processes which form part of the present invention. In the methods below, R<sup>0</sup>, R<sup>1</sup>, and R<sup>2</sup> are

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as defined in formula (I) above unless otherwise indicated.

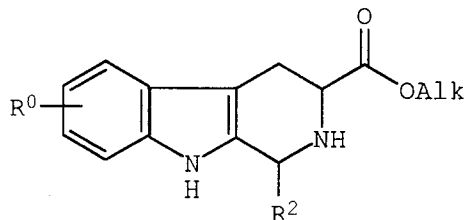
Thus, a process (A) for preparing a compound of formula (I) wherein R<sup>3</sup> represents hydrogen comprises treating a compound of formula (II)



(II)

in which Alk represents C<sub>1-6</sub>alkyl, e.g., methyl or ethyl, and Hal is a halogen atom, e.g., chlorine, with a primary amine R<sup>1</sup>NH<sub>2</sub> in a suitable solvent, such as an alcohol (e.g., methanol or ethanol) or a mixture of solvents, conveniently at a temperature of from 20°C to reflux (e.g., at about 50°C).

A compound of formula (II) can be conveniently prepared by treating a compound of formula (III)



(III)

- 30 -

with a haloacetyl halide (e.g., chloroacetyl chloride) in a suitable solvent, such as a halogenated hydrocarbon (e.g., trichloromethane or dichloromethane) or an ether (e.g., tetrahydrofuran), preferably in the presence of a base such as an organic amine (e.g., a trialkylamine such as triethylamine) or an alkali metal carbonate or bicarbonate (e.g.,  $\text{NaHCO}_3$ ). The reaction conveniently can be effected at a temperature of from  $-20^\circ\text{C}$  to  $+20^\circ\text{C}$  (e.g., at about  $0^\circ\text{C}$ ).

A compound of formula (I) also can be prepared from a compound of formula (III) in a two-step procedure via a compound of formula (II) isolated without purification.

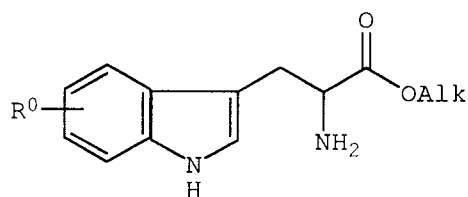
Compounds of formula (I) can be prepared as individual enantiomers in two steps from the appropriate enantiomer of formula (III) or as mixtures (e.g., racemates) of either pairs of cis or trans isomers from the corresponding mixtures of either pairs of cis or trans isomers of formula (III).

Individual enantiomers of the compounds of the invention can be prepared from racemates by resolution using methods known in the art for the separation of racemic mixtures into their constituent enantiomers, for examples, using HPLC (high performance liquid chromatography) on a chiral column such as Hypersil naphthylurea.

A compound of formula (III) conveniently can be prepared from a tryptophan alkyl ester of formula (IV)



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(IV)

(where  $Alk$  is as previously defined) or a salt thereof (e.g., the hydrochloride salt) according to either of the following procedures (a) and (b). Procedure (b) is only suitable for preparing cis isomers of formula (III) and can be particularly suitable for preparing individual cis enantiomers of formula (III) from D- or L- tryptophan alkyl esters as appropriate.

Procedure (a)

This comprises a Pictet-Spengler cyclization between a compound of formula (IV) and an aldehyde  $R^2CHO$ . The reaction can be conveniently effected in a suitable solvent such as a halogenated hydrocarbon (e.g., dichloromethane) or an aromatic hydrocarbon (e.g., toluene) in the presence of an acid, such as trifluoroacetic acid. The reaction conveniently can be carried out at a temperature of from  $-20^\circ C$  to reflux to provide a compound of formula (III) in one step. The reaction also can be carried out in a solvent such as an aromatic hydrocarbon (e.g., benzene or toluene) under reflux, optionally using a Dean-Stark apparatus to trap the water produced.

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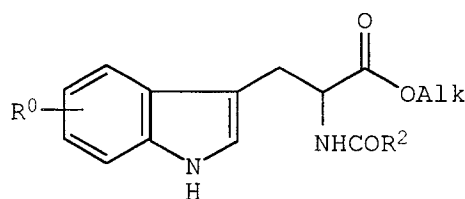
The reaction provides a mixture of cis and trans isomers which can be either individual enantiomers or racemates of pairs of cis or trans isomers, depending upon whether racemic or enantiomerically pure tryptophan alkyl ester was used as the starting material. Individual cis or trans enantiomers conveniently can be separated from mixtures thereof by fractional crystallization or by chromatography (e.g., flash column chromatography) using appropriate solvents and eluents. Similarly, pairs of cis and trans isomers can be separated by chromatography (e.g., flash column chromatography) using appropriate eluents. An optically pure trans isomer also can be converted to an optically pure cis isomer using suitable epimerization procedures. One such procedure comprises treating the trans isomer or a mixture (e.g., 1:1 mixture) of cis and trans isomers with methanolic or aqueous hydrogen chloride at a temperature of from 0°C to the refluxing temperature of the solution. The mixture then can be subjected to chromatography (e.g., flash column chromatography) to separate the resulting diastereoisomers, or in the procedure utilizing aqueous hydrogen chloride, the desired cis isomer precipitates out as the hydrochloride salt which then can be isolated by filtration.

#### Procedure (b)

This comprises a four-step procedure from a compound of formula (IV) or a salt thereof (e.g., the hydrochloride salt). The procedure is particularly suitable for preparing a 1R, 3R isomer of

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formula (III) from a D-tryptophan alkyl ester of  
formula (IV) or a salt thereof (e.g., the hydro-  
chloride salt). Thus, a first step (i) comprises  
treating a compound of formula (IV) with an acid  
halide  $R^2COHal$  (where Hal is as previously defined)  
in the presence of a base, e.g., an organic base  
such as a trialkylamine (for example, triethyl-  
amine), to provide a compound of formula (V).

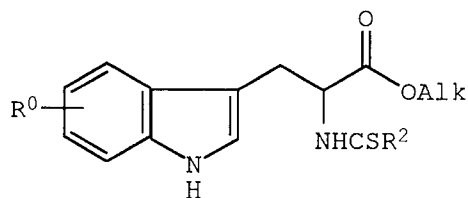


(V)

The reaction can be conveniently carried  
out in a suitable solvent, such as a halogenated  
hydrocarbon (e.g., dichloromethane) or an ether  
(e.g., tetrahydrofuran), and at a temperature of  
from  $-20^{\circ}C$  to  $+40^{\circ}C$ .

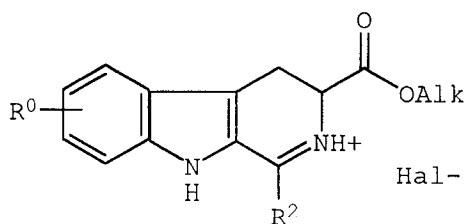
Step (ii) comprises treating a compound of  
formula (V) with an agent to convert the amide group  
to a thioamide group. Suitable sulfurating agents  
are well known in the art. Thus, for example, the  
reaction can be conveniently effected by treating  
(V) with Lawesson's reagent. This reaction can be  
conveniently carried out in a suitable solvent, such  
as ether (e.g., dimethoxyethane) or an aromatic  
hydrocarbon (e.g., toluene), at an elevated temper-  
ature, such as from  $40^{\circ}C$  to  $80^{\circ}C$  to provide a com-  
pound of formula (VI)

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(VI)

Step (iii) comprises treating a compound of formula (VI) with a suitable agent to provide a compound of formula (VII)



(VII)

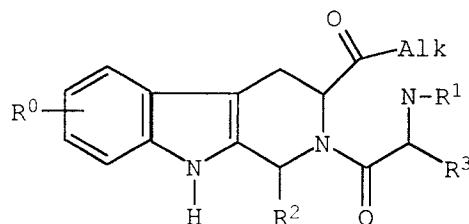
wherein Hal is a halogen atom, e.g., iodine. The reaction can be conveniently effected by treating (VI) with an alkylating agent, such as a methyl halide (e.g., methyl iodide), or an acylating agent, such as an acetyl halide (e.g., acetyl chloride), in a suitable solvent, such as a halogenated hydrocarbon (e.g., dichloromethane) at an elevated temperature (e.g., under reflux).

In step (iv), the resulting iminium halide of formula (VII) can be treated with a reducing agent, such as a boron hydride, e.g., sodium borohydride, to provide the desired compound of formula (III). The reduction can be conveniently effected

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at a low temperature, e.g., within the range of -100°C to 0°C, in a suitable solvent, such as an alcohol (e.g., methanol).

There is further provided by the present invention a process (B) for preparing a compound of formula (I), wherein R<sup>1</sup> and R<sup>3</sup> together represent a 3- or 4-membered alkyl or alkenyl chain, which process (B) comprises cyclization of a compound of formula (VIII)

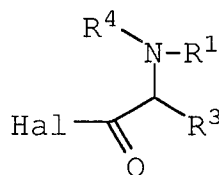


(VIII)

wherein Alk represents C<sub>1-6</sub>alkyl and R<sup>1</sup> and R<sup>3</sup> together represent a 3- or 4-membered chain, both as hereinbefore described. The cyclization is suitably carried out in an organic solvent or solvents, such as an alcoholic solvent (e.g., methanol), and optionally an ether solvent such as tetrahydrofuran, and in the presence of a reducing agent, aptly a palladium catalyst, such as palladium on carbon.

Conveniently, a compound of formula (VIII) is prepared by reaction of a compound of formula (III) as hereinbefore described with a compound of formula (IX)

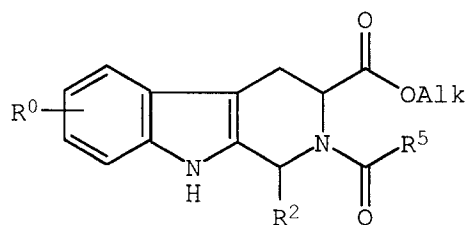
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(IX)

wherein Hal represents a halogen atom as hereinbefore described, R<sup>1</sup> and R<sup>3</sup> together represent a 3- or 4-membered chain as hereinbefore described, and R<sup>4</sup> represents a protecting group, suitably a benzyloxy-carbonyl group or the like. Typically, the reaction is carried out in a chlorinated organic solvent, such as dichloromethane, and a tertiary amine, such as triethylamine or the like.

According to a further aspect of the present invention, there is provided a process (C) for preparing a compound of formula (I) wherein R<sup>3</sup> represents C<sub>1-3</sub>alkyl, which process comprises cyclization of a compound of formula (X)



(X)

wherein Alk represents C<sub>1-6</sub>alkyl as hereinbefore described and R<sup>5</sup> represents C<sub>2-5</sub>alkyl, substituted at C<sub>1</sub> by a halogen atom, the halogen atom being as

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hereinbefore described. Suitably, the cyclization is achieved by reflux for many hours, such as 22 to 26 hours, in the presence of an ether solvent, such as tetrahydrofuran, and a suitable amine as hereinafter described in the accompanying examples. —

Aptly, a compound of formula (X) can be prepared from a compound of formula (III) by suitable acylation techniques, such as reaction with a C<sub>3-6</sub> carboxylic acid, substituted at C-2 by a halogen atom in a halogenated organic solvent, such as dichloromethane.

Compounds of formula (I) can be converted to other compounds of formula (I). Thus, for example, when R<sup>2</sup> is a substituted benzene ring, it may be necessary or desirable to prepare the suitably substituted compound of formula (I) subsequent to process (A), (B), or (C), as above. Examples of appropriate interconversions include nitro to amino or aralkyloxy to hydroxy by suitable reducing means (e.g., using a reducing agent such as SnCl<sub>2</sub> or a palladium catalyst, such as palladium-on-carbon), or amino to substituted amino, such as acylamino or sulphonylamino using standard acylating or sulphonylating conditions. In the case where R<sup>2</sup> represents a substituted bicyclic system, suitable interconversion can involve removal of a substituent, such as by treatment with a palladium catalyst (e.g., palladium-on-carbon) whereby, for example, a benzyl substituent can be removed from a suitable bicyclic system.

The pharmaceutically acceptable acid addition salts of the compounds of formula (I), which contain a basic center, can be treated with a

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suitable acid, either neat or in a suitable solution, and the resulting salt isolated either by filtration or by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts can be obtained in an analogous manner by treating a solution of a compound of formula (I) with a suitable base. Both types of salt can be formed or interconverted using ion-exchange resin techniques.

Compounds of the invention can be isolated in association with solvent molecules by crystallization from or evaporation of an appropriate solvent.

Thus, according to a further aspect of the invention, we provide a process for preparing a compound of formula (I) or a salt or solvate (e.g., hydrate) thereof which comprises process (A), (B), or (C) as hereinbefore described followed by

- (i) an interconversion step, and/or
- (ii) salt formation, or
- (iii) solvate (e.g., hydrate) formation.

There is further provided by the present invention compounds of formulae (II), (VIII), (X), and further compounds of formulae (III), (V), (VI), and (VII), with the exception for compounds (III), (V), (VI), and (VII), wherein  $R^0$  is hydrogen,  $R^2$  is phenyl, and Alk is methyl.

The pharmaceutically acceptable acid addition salts of the compounds of formula (I) which contain a basic center can be prepared in a conventional manner. For example, a solution of the free base can be treated with a suitable acid, either



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neat or in a suitable solution, and the resulting salt isolated either by filtration or by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts can be obtained in an analogous manner by treating a solution of a compound of formula (I) with a suitable base. Both types of salt can be formed or interconverted using ion-exchange resin techniques.

Thus, according to a further aspect of the invention, a method for preparing a compound of formula (I) or a salt or solvate (e.g., hydrate) is provided, wherein the method comprises process (A), (B), or (C) as hereinbefore described, followed by (i) salt formation, or (ii) solvate (e.g., hydrate) formation. The method of preparing the following Intermediates 1 through 92 and Examples 1 through 125, and characterization of the compounds, can be found in published PCT applications WO 95/19978, WO 97/03985, and WO 97/03675, incorporated herein by reference.

Intermediates 1 and 2

Methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediates 3 and 4

Methyl 1,2,3,4-tetrahydro-1-(4-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

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Intermediate 5

Methyl 1,2,3,4-tetrahydro-1-(3-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer

5 Intermediates 6 and 7

Methyl 1,2,3,4-tetrahydro-1-(4-ethoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

10 Intermediates 8 and 9

Methyl 1,2,3,4-tetrahydro-1-(2,3-dihydrobenzo[b]-furan-5-yl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

15 Intermediates 10 and 11

Methyl 1,2,3,4-tetrahydro-1-(3,4-ethylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

20 Intermediate 12

Methyl 1,2,3,4-tetrahydro-1-(2-chlorophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, mixture of cis and trans isomers

25 Intermediates 13 and 14

Methyl 1,2,3,4-tetrahydro-1-(4-chlorophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

30 Intermediates 15 and 16

Methyl 1,2,3,4-tetrahydro-1-(3,4-dichlorophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

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Intermediate 17

Methyl 1,2,3,4-tetrahydro-1-(1,2,3,4-tetrahydro-6-naphthyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer

5

Intermediates 18 and 19

Methyl 1,2,3,4-tetrahydro-1-(2-naphthyl)-9H-pyrido-[3,4-b]indole-3-carboxylate, cis and trans isomers

10

Intermediates 20 and 21

Methyl 1,2,3,4-tetrahydro-1-(2-thienyl)-9H-pyrido-[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediates 22 and 23

15

Ethyl 1,2,3,4-tetrahydro-1-(3-thienyl)-9H-pyrido-[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediates 24 and 25

20

Methyl 1,2,3,4-tetrahydro-1-(5-bromo-2-thienyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediates 26 and 27

25

Methyl 1,2,3,4-tetrahydro-1-(4-bromo-2-thienyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediate 28

30

Methyl 1,2,3,4-tetrahydro-1-(3-furyl)-9H-pyrido[3,4-b]indole-3-carboxylate, mixture of cis and trans isomers

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Intermediates 29 and 30

Ethyl 1,2,3,4-tetrahydro-1-(5-methyl-2-furyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

5

Intermediates 31 and 32

Ethyl 1,2,3,4-tetrahydro-1-(4-methylphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

10

Intermediates 33 and 34

Methyl 1,2,3,4-tetrahydro-1-(3-methylphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

15

Intermediates 35 and 36

Methyl 1,2,3,4-tetrahydro-1-(4-trifluoromethylphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

20

Intermediates 37 and 38

Ethyl 1,2,3,4-tetrahydro-1-(4-cyanophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

25

Intermediate 39

Methyl 1,2,3,4-tetrahydro-1-(4-hydroxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer

30

Intermediate 40

Methyl 1,2,3,4-tetrahydro-1-(3-hydroxy-4-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer

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Intermediate 41

Methyl 1,2,3,4-tetrahydro-1-(4-hydroxy-3-methoxy-phenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer

5

Intermediate 42

Methyl 1,2,3,4-tetrahydro-1-(4-ethylphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

10

Intermediates 43 and 44

Methyl 1,2,3,4-tetrahydro-1-(4-isopropylphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

15

Intermediates 45 and 46

Ethyl 1,2,3,4-tetrahydro-1-(4-nitrophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

20

Intermediate 47

Ethyl 1,2,3,4-tetrahydro-1-(4-dimethylaminophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, mixture of cis and trans isomers

25

Intermediates 48 and 49

Ethyl 1,2,3,4-tetrahydro-1-(3-pyridyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

30

Intermediates 50 and 51

Methyl 1,2,3,4 tetrahydro-6-fluoro-1-(3,4-methylene-dioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

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Intermediates 52 and 53

Methyl 1,2,3,4-tetrahydro-6-fluoro-1-(4-methoxy-phenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

5

Intermediates 54 and 55

(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(3,4-methylene-dioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and

10 (1S,3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylene-dioxy-phenyl)-9H-pyrido[3,4-b]indole-3-carboxylate trans isomer

Intermediate 56

15 (1S, 3S) Methyl-1,2,3,4-tetrahydro-1-(3,4-methylene-dioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and

(1R, 3S) methyl-1,2,3,4-tetrahydro-1-(3,4-methylene-dioxy-phenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, trans isomer

20

Intermediates 57 and 58

(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(4-methoxy-phenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and

25

(1S,3R)-methyl 1,2,3,4-tetrahydro-1-(4-methoxy-phenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, trans isomer

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Intermediates 59 and 60

(1R, 3R)-Methyl 1,2,3,4-tetrahydro-1-(3-chloro-4-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and

5 (1S, 3R)-methyl 1,2,3,4-tetrahydro-1-(3-chloro-4-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, trans isomer

Intermediates 61 and 62

10 (1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(2,3-dihydrobenzo[b]furan-5-yl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and

(1S,3R)-methyl 1,2,3,4-tetrahydro-1-(5-(2,3-dihydrobenzo[b]furan))-9H-pyrido[3,4-b]indole-3-carboxylate, trans isomer

15

Intermediates 63 and 64

(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(5-indanyl)-9H-pyrido[3,4-b]indole-3-carboxylate cis isomer and

20 (1S,3R)-methyl 1,2,3,4-tetrahydro-1-(5-indanyl)-9H-pyrido[3,4-b]indole-3-carboxylate trans isomer

Intermediate 65

25 Ethyl 1,2,3,4-tetrahydro-1-(4-trifluoromethoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediate 66

30 Methyl 1,2,3,4-tetrahydro-1-(5-methyl-2-thienyl)-9H-pyrido [3,4-b]indole-3-carboxylate, cis and trans isomers

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Intermediates 67 and 68

(1S,3R)-Methyl 1,2,3,4-tetrahydro-1-(3,4-methylene-  
dioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate  
and

5 (1R,3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylene-  
dioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

Intermediate 69

10 (1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(3,4-methylene-  
dioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

Intermediate 70

(R)-N<sup>α</sup>-(3,4-Methylenedioxyphenylcarbonyl)-tryptophan  
methyl ester

15

Intermediate 71

(R)-N<sup>α</sup>-(3,4-Methylenedioxyphenylthiocarbonyl)-trypto-  
phan methyl ester

20

Intermediate 72

(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(3,4-methylene-  
dioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

Intermediate 73

25 (1R,3R)-Methyl 1,2,3,4-tetrahydro-2-chloroacetyl-  
(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-  
carboxylate

Intermediate 74

30 Methyl 1,2,3,4-tetrahydro-6-methyl-1-(3,4-methylene-  
dioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate,  
cis and trans isomers



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Intermediates 75 and 76

- (1R, 3R)-Methyl 1,2,3,4-tetrahydro-1-(7-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazinyl))-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and (1S, 3R)-Methyl 1,2,3,4-tetrahydro-1-(7-(4-methyl-3,4-dihydro-2H-benzo[1,4]-oxazinyl))-9H-pyrido[3,4-b]indole-3-carboxylate, trans isomer

Intermediate 77

- Methyl 1,2,3,4-tetrahydro-1-(5-(N-benzylindolinyl))-9H-pyrido[3,4-b]indole-3-carboxylate, mixture of (1R, 3R) and (1S, 3R) isomers

Intermediates 78 and 79

- (1R, 3R)-Methyl 1,2,3,4-tetrahydro-1-(4-carbomethoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and (1S, 3R)-methyl 1,2,3,4-tetrahydro-1-(4-carbomethoxy-phenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, trans isomer

Intermediate 80

- (1R, 3R)-Methyl 1,2,3,4-tetrahydro-2-[2-(benzyloxy-carbonyl)-R-prolyl]-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

Intermediate 81

- (1R, 3R)-Methyl 1,2,3,4-tetrahydro-2-[2-(benzyloxy-carbonyl)-S-prolyl]-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

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## Intermediate 82

(1R, 3R)-Methyl 1,2,3,4-tetrahydro-2-(2-chloro-propionyl)-1-(3,4-methylenedioxyphenyl)-9H-pyrido-[3,4-b]indole-3-carboxylate

5

## Intermediate 83

(1R, 3R)-Methyl 1,2,3,4-tetrahydro-2-(2-chloro-propionyl)-1-(3,4-methylenedioxyphenyl)-9H-pyrido-[3,4-b]indole-3-carboxylate

10

## Intermediates 84 and 85

(1R, 3R)-Methyl 1,2,3,4-tetrahydro-1-(3,4-dibenzyl-oxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate cis isomer and (1S, 3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-dibenzyl-oxyphenyl)-9H-pyrido [3,4-b]indole-3-carboxylate trans isomer

15

## Intermediate 86

(6R, 12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-dibenzyl-oxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

20

## Intermediate 87

Methyl 1,2,3,4-tetrahydro-1-(5-(2-methylisoindol-1-yl))-9H-pyrido[3,4-b]indole-3-carboxylate, mixture of (1R,3R) and (1S,3R) isomers

25

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Intermediates 88 and 89

(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(5-benzofuranyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and

5 (1S,3R)-methyl 1,2,3,4-tetrahydro-1-(5-benzofuranyl)-9H-pyrido[3,4-b]indole-3-carboxylate trans isomer

Intermediate 90

10 (1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(5-benzofuranyl)-2-chloroacetyl-9H-pyrido[3,4-b]indole-3-carboxylate

Intermediate 91

15 (1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(5-benzofuranyl)-2-(2-(S)-benzyloxycarbonylaminopropionyl)-9H-pyrido[3,4-b]indole-3-carboxylate

Intermediate 92

20 (1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(5-benzofuranyl)-2-[2-(S)-benzyloxycarbonylmethylamino)propionyl]-9H-pyrido[3,4-b]indole-3-carboxylate

25 Example 1

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylene-dioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from Intermediate 1 and methylamine.

30

The following compounds were obtained in a similar manner:

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## Example 2

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-10-fluoro-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]-indole-1,4-dione--from butylamine and Intermediate 52.

## Example 3

Trans-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 2.

## Example 4

Cis-2,3,6,7,12,12a-hexahydro-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from ammonia and Intermediate 1.

## Example 5

Cis-2,3,6,7,12,12a-hexahydro-10-fluoro-6-(4-methoxyphenyl)-2-(2,2,2-trifluoroethyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from 2,2,2-trifluoroethylamine and Intermediate 52.

## Example 6

Cis-2,3,6,7,12,12a-hexahydro-10-fluoro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 50.

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## Example 7

(6R, 12aS)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6.1]pyrido[3,4-b]indole-1,4-dione--from methylamine and the trans  
5 isomer of Intermediate 56.

## Example 8

(6S, 12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino [2',1':6.1]pyrido-  
10 [3,4-b]indole-1,4-dione--from methylamine and Intermediate 55.

## Example 9

Cis-2, 3, 6, 7, 12, 12a-hexahydro-2-[2-(2-pyridyl)-ethyl]-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1'-  
15 6,1]pyrido[3,4-b]indole-1,4-dione--from 2-(2-pyridyl)ethylamine and Intermediate 1.

## Example 10

Cis-2,3,6,7,12,12a-hexahydro-2-(2-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-  
20 pyrido[3,4-b]indole-1,4-dione--from 2-pyridylmethylamine and Intermediate 1.

## 25 Example 11

Cis-2,3,6,7,12,12a-hexahydro-2-(3-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-  
pyrido[3,4-b]indole-1,4-dione--from 3-pyridylmethyl-  
amine and Intermediate 1.

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## Example 12

Cis-2,3,6,7,12,12a-hexahydro-2-(4-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from 4-pyridylmethyl-amine and Intermediate 1.

## Example 13

Cis-2,3,6,7,12,12a-hexahydro-2-ethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione--from ethylamine and Intermediate 1.

## Example 14

Cis-2,3,6,7,12,12a-hexahydro-2-(2,2,2-trifluoroethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from 2,2,2-trifluoroethylamine and Intermediate 1.

## Example 15

Cis-2,3,6,7,12,12a-hexahydro-6-(3,4-methylenedioxyphenyl)-2-propyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from propylamine and Intermediate 1.

## Example 16

Cis-2,3,6,7,12,12a-hexahydro-2-isopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from isopropylamine and Intermediate 1.

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## Example 17

Cis-2,3,6,7,12,12a-hexahydro-2-cyclopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from cyclopropylamine and Intermediate 1.

## Example 18

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from butylamine and Intermediate 1.

## Example 19

Trans-2,3,6,7,12,12a-hexahydro-2-butyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from butylamine and Intermediate 2.

## Example 20

Cis-2,3,6,7,12,12a-hexahydro-2-cyclopropylmethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from cyclopropylmethylamine and Intermediate 1.

## Example 21

Cis-2,3,6,7,12,12a-hexahydro-2-cyclopentyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from cyclopentylamine and Intermediate 1.

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## Example 22

Cis-2,3,6,7,12,12a-hexahydro-2-cyclohexyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from cyclohexylamine and  
5 Intermediate 1.

## Example 23

Cis-2,3,6,7,12,12a-hexahydro-2-benzyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from benzylamine and Interme-  
10 diate 1.

## Example 24

Cis-2,3,6,7,12,12a-hexahydro-2-(4-fluorobenzyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-  
15 pyrido[3,4-b]indole-1,4-dione--from 4-fluorobenzylamine and Intermediate 1.

## Example 25

Cis-2,3,6,7,12,12a-hexahydro-6-(4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 3.

## Example 26

25 Trans-2,3,6,7,12,12a-hexahydro-6-(4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 4.

## Example 27

30 Cis-2,3,6,7,12,12a-hexahydro-2-ethyl-6-(4-methoxyphenyl)pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from ethylamine and Intermediate 3.



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## Example 28

Cis-2,3,6,7,12,12a-hexahydro-6-(4-methoxyphenyl)-2-(2,2,2-trifluoroethyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from 2,2,2-trifluoroethylamine and Intermediate 3.

## Example 29

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from butylamine and Intermediate 3.

## Example 30

Trans-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from butylamine and Intermediate 4.

## Example 31

Cis-2,3,6,7,12,12a-hexahydro-6-(4-methoxyphenyl)-2-cyclopropylmethylpyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from cyclopropylmethylamine and Intermediate 3.

## Example 32

Cis-2,3,6,7,12,12a-hexahydro-2-benzyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from benzylamine and Intermediate 3.

## Example 33

Cis-2,3,6,7,12,12a-hexahydro-6-(3-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 5.

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## Example 34

Cis-2,3,6,7,12,12a-hexahydro-6-(4-ethoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 6.

5

## Example 35

Cis-2,3,6,7,12,12a-hexahydro-6-(4-ethoxyphenyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from cyclopropylmethylamine and Intermediate 6.

10

## Example 36

Cis-2,3,6,7,12,12a-hexahydro-6-(2,3-dihydrobenzo[b]-furan-5-yl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 8.

15

## Example 37

Cis-2,3,6,7,12,12a-hexahydro-6-(2,3-dihydrobenzo[b]-furan-5-yl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from cyclopropylmethylamine and Intermediate 8.

20

## Example 38

Cis-2,3,6,7,12,12a-hexahydro-6-(3,4-ethylenedioxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 10.

25

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## Example 39

Cis-2,3,6,7,12,12a-hexahydro-6-(3,4-ethylenedi-  
oxyphenyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]-  
pyrido[3,4-b]indole-1,4-dione--from cyclopropyl-  
5 methylamine and Intermediate 10.

## Example 40

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(2-chloro-  
phenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-  
10 dione--from butylamine and Intermediate 12.

## Example 41

Cis-2,3,6,7,12,12a-hexahydro-6-(4-chlorophenyl)-2-  
methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-  
15 dione--from methylamine and Intermediate 13.

## Example 42

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-chloro-  
phenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-  
20 dione--from butylamine and Intermediate 13.

## Example 43

Cis-2,3,6,7,12,12a-hexahydro-6-(3,4-dichlorophenyl)-  
2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-  
25 dione--from methylamine and Intermediate 15.

## Example 44

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-phenyl-  
pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-  
30 dione--from butylamine and cis-methyl 1,2,3,4-tetra-  
hydro-1-phenyl-9H-pyrido[3,4-b]indole-3-carboxylate.

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## Example 45

Cis-2,3,6,7,12,12a-hexahydro-2-benzyl-6-phenyl-  
pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-  
dione--from benzylamine and cis-methyl-1,2,3,4-  
5 tetrahydro-1-phenyl-9H-pyrido[3,4-b]indole-3-  
carboxylate.

## Example 46

Trans-2,3,6,7,12,12a-hexahydro-2-benzyl-6-phenyl-  
10 pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-  
dione--from benzylamine and cis-methyl-1,2,3,4-  
tetrahydro-1-phenyl-9H-pyrido[3,4-b]indole-3-  
carboxylate.

## 15 Example 47

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(1,2,3,4-  
tetrahydro-6-naphthyl)-pyrazino[2',1':6,1]pyrido-  
[3,4-b]indole-1,4-dione--from methylamine and  
Intermediate 17.

20

## Example 48

Cis-2,3,6,7,12,12a-hexahydro-2-isopropyl-6-(1,2,3,4-  
tetrahydro-6-naphthyl)-pyrazino[2',1':6,1]pyrido-  
[3,4-b]indole-1,4-dione--from isopropylamine and  
25 Intermediate 17.

## Example 49

Cis-2,3,6,7,12,12a-hexahydro-2-cyclopropylmethyl-6-  
(1,2,3,4-tetrahydro-6-naphthyl)-pyrazino[2',1':-  
30 6,1]pyrido[3,4-b]indole-1,4-dione--from cyclopropyl-  
methylamine and Intermediate 17.

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## Example 50

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(2-naphthyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 18.

5

## Example 51

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(2-thienyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from butylamine and Intermediate 20.

10

## Example 52

Cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 24.

15

## Example 53

Cis-2,3,6,7,12,12a-hexahydro-6-(4-bromo-2-thienyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 26.

20

## Example 54

Cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from cyclopropylmethylamine and Intermediate 24.

25

## Example 55

Cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-cyclopentyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from cyclopentylamine and Intermediate 24.

30

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## Example 56

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(5-methyl-2-thienyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and the cis isomer of  
5 Intermediate 66.

## Example 57

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3-thienyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 22.  
10

## Example 58

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(3-thienyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from butylamine and Intermediate 22.  
15

## Example 59

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3-furyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and the cis isomer of  
20 Intermediate 28.

## Example 60

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(5-methyl-2-furyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 29.  
25

## Example 61

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 31.  
30

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## Example 62

Cis-2,3,6,7,12,12a-hexahydro-2-isopropyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]-indole-1,4-dione--from isopropylamine and  
5 Intermediate 31.

## Example 63

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from butylamine and Intermediate 31.  
10

## Example 64

Cis-2,3,6,7,12,12a-hexahydro-2-cyclopropylmethyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]-indole-1,4-dione--from cyclopropylmethylamine and  
15 Intermediate 31.

## Example 65

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 33.  
20

## Example 66

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-trifluoromethylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]-indole-1,4-dione--from butylamine and Intermediate  
25 35.

## Example 67

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(4-trifluoromethoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and the cis isomer of Intermediate 65.  
30

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## Example 68

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(4-hydroxy-phenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 39.

5

## Example 69

Cis-2,3,6,7,12,12a-hexahydro-6-(3-hydroxy-4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 40.

10

## Example 70

Cis-2,3,6,7,12,12a-hexahydro-6-(4-hydroxy-3-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 41.

15

## Example 71

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-cyanophenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from butylamine and Intermediate 37.

20

## Example 72

Cis-2,3,6,7,12,12a-hexahydro-6-(4-ethylphenyl)-2-isopropyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from isopropylamine and the cis isomer of Intermediate 42.

25

## Example 73

Cis-2,3,6,7,12,12a-hexahydro-6-(4-ethylphenyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from cyclopropylmethylamine and the cis isomer of Intermediate 42.

30



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## Example 74

Cis-2,3,6,7,12,12a-hexahydro-6-(4-isopropylphenyl)-  
2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-  
dione--from methylamine and Intermediate 43.

5

## Example 75

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-nitro-  
phenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-  
dione--from butylamine and Intermediate 45.

10

## Example 76

Cis-2,3,6,7,12,12a-hexahydro-6-(4-dimethylamino-  
phenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-  
b]indole-1,4-dione--from methylamine and the cis  
isomer of Intermediate 47.

15

## Example 77

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3-pyridyl)-  
pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-  
dione--from methylamine and Intermediate 48.

20

## Example 78

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-  
methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-  
b]indole-1,4-dione--Intermediate 54 and methylamine.

25

The following compounds were obtained in a  
similar manner:

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## Example 79

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-isopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from isopropylamine  
5 and Intermediate 54.

## Example 80

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-butyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from butylamine and Interme-  
10 diate 54.

## Example 81

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-isobutyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from isobutylamine  
15 and Intermediate 54.

## Example 82

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopentyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from cyclopentylamine  
20 and Intermediate 54.

## 25 Example 83

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-methylene-dioxyphenyl)-2-cyclohexylmethyl-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from cyclohexyl-methylamine and the cis isomer of Intermediate 56.  
30

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## Example 84

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopropyl-methyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from cyclopropyl-methylamine and Intermediate 57.

## Example 85

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-butyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from butylamine and Intermediate 57.

## Example 86

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopentyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--rom cyclopentylamine and Intermediate 57.

## Example 87

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3-chloro-4-methoxyphenyl)-2-cyclopropylmethyl-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from cyclopropylmethylamine and Intermediate 59.

## Example 88

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopentyl-6-(3-chloro-4-methoxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from cyclopentylamine and Intermediate 59.

30

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## Example 89

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3-chloro-4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido-[3,4-b]indole-1,4-dione--from methylamine and  
5 Intermediate 59.

## Example 90

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-isopropyl-6-(3-chloro-4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido-[3,4-b]indole-1,4-dione--from isopropylamine and  
10 Intermediate 59.

## Example 91

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(2,3-dihydro-benzo[b]furan-5-yl)-2-methyl-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from methylamine and  
15 Intermediate 61.

## Example 92

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(2,3-dihydro-benzo[b]furan-5-yl)-2-methylcyclopropyl-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from  
20 methylcyclopropylamine and Intermediate 61.

## 25 Example 93

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-indanyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 63.

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## Example 94

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-indanyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from cyclopropylmethylamine and  
5 Intermediate 63.

## Example 95

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from Intermediate 73 and methyl-  
10 amine.

## Example 96

Cis-2,3,6,7,12,12a-hexahydro-2,10-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from the same procedure used to  
15 prepare Example 1, but starting from methylamine and the cis isomer of Intermediate 74.

## 20 Example 97

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-(3,4-dimethoxybenzyl)-6-(3,4-methylenedioxyphenyl)-pyrazino-  
[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from the  
25 same procedure as used to prepare Example 78, but starting from veratrylamine and Intermediate 54.

## Example 98

Cis-2,3,6,7,12,12a-hexahydro-6-(4-aminophenyl)-2-butyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-  
30 dione--from Example 75.

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## Example 99

Cis-2,3,6,7,12,12a-hexahydro-6-(4-acetamidophenyl)-  
2-butyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-  
dione--from Example 98.

5

## Example 100

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methyl-  
sulfonamidophenyl)-pyrazino[2',1':6,1]pyrido[3,4-  
b]indole-1,4-dione--from Example 98.

10

## Example 101

(6R, 12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-methyl-  
enedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]-  
indole-1,4-dione--from the same procedure as Example  
100 starting from ammonia and Intermediate 54.

15

## Example 102

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-methylene-  
dioxyphenyl)-2-(2-propynyl)-pyrazino[2',1':6,1]-  
pyrido[3,4-b]indole-1,4-dione--from the same pro-  
cedure as Example 100 starting from propargylamine  
and Intermediate 54.

20

## Example 103

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-(3,4-methylene-  
dioxybenzyl)-6-(3,4-methylenedioxyphenyl)-pyrazino-  
[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from the  
same procedure as Example 100 starting from piper-  
onylamine and Intermediate 54.

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## Example 104

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-(3,4-dimethoxyphenethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from the same procedure as Example 100 3,4-dimethoxyphenethylamine and Intermediate 54.

## Example 105

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-furfuryl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from the same procedure as Example 100 starting from furfurylamine and Intermediate 54.

## Example 106

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-methylenedioxyphenyl)-2-(2-thienylmethyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from the same procedure as Example 100 starting from 2-thiophenemethylamine and Intermediate 54.

## Example 107

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from the same procedure as Example 100 starting from methylamine and Intermediate 57.

## Example 108

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-ethyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from the same procedure as Example 100 starting from ethylamine and Intermediate 57.

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## Example 109

(6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(7-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazinyl))-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--  
5 from the same procedure as Example 100 starting from Intermediate 75.

## Example 110

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-(N-benzyl-indoliny1))-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from the same procedure as  
10 Example 100 starting from Intermediate 77.

## Example 111

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-indoliny1)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from Example 110.  
15

## Example 112

Cis-2,3,6,7,12,12a-hexahydro-6-(4-ethylphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from the same procedure as Example 100 starting from methylamine and the cis isomer of Intermediate 42.  
20

25

## Example 113

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(4-carbomethoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from the same procedure as  
30 Example 100 starting from Intermediate 78 (cis isomer) and methylamine.



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## Example 114

(5aR,12R,14aR)-1,2,3,5a,6,11,12,14a-Octahydro-12-(3,4-methylenedioxyphenyl)-pyrrolo[1'',2'':4',5']-pyrazino[2',1':6,1]pyrido[3,4-b]indole-5-1,4-dione--  
5 from Intermediate 80.

## Example 115

(5aR,12R,14aS)-1,2,3,5,6,11,12,14a-Octahydro-12-(3,4-methylenedioxyphenyl)-pyrrolo[1'',2'':4',5']-  
10 pyrazino[2',1':6,1]pyrido[3,4-b]indole-5-1,4-dione--  
from Intermediate 81.

## Example 116

(3R,6R,12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-  
15 6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-  
pyrido[3,4-b]indole-1,4-dione--from Intermediate 82  
and methylamine.

## Example 117

(3S,6R,12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-  
20 6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-  
pyrido[3,4-b]indole-1,4-dione--from Intermediate 83  
and methylamine.

## 25 Example 118

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-dihydroxy-phenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]-  
indole-1,4-dione--from Intermediate 86.

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## Example 119

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(5-(2-methylisoindoliny1))pyrazino[2',1':6,1]pyrido[3,4b]indole-1,4-dione--from Intermediate 87 and methyl-  
5 amine.

## Example 120

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-benzofuranyl)-2-methyl-pyrazino[2'1':6,1]pyrido[3,4-b]indole-1,4-dione--and Intermediate 91 and methyl-  
10 amine.

## Example 121

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-benzofuranyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from ammonia and Intermediate 91.  
15

## Example 122

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-benzofuranyl)-2-isopropyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from Intermediate 91.  
20

## Example 123

(3S,6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-benzofuranyl)-3-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from Intermediate 92.  
25

## Example 124

(3S,6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(t-benzofuranyl)-2,3-dimethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from Intermediate 93.  
30

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Example 125

(3S, 6R, 12aR)-2, 3, 6, 7, 12, 12a-Hexahydro-3-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from Intermediate 43 and ammonia.

**TABLETS FOR ORAL ADMINISTRATION****A. Direct Compression**

1.	mg/tablet
Active Ingredient	50.0
Crospovidone USNF	8.0
Magnesium Stearate Ph Eur	1.0
Anhydrous Lactose	141.0

The active ingredient was sieved and blended with the excipients. The resultant mix was compressed into tablets.

2.	mg/tablet
Active Ingredient	50.0
Colloidal Silicon Dioxide	0.5
Crospovidone	8.0
Sodium Lauryl Sulfate	1.0
Magnesium Stearate Ph Eur	1.0
Microcrystalline Cellulose USNF	139.5

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The active ingredient was sieved and blended with the excipients. The resultant mix was compressed into tablets.

5           B.           Wet Granulation

	1.	mg/tablet
	Active ingredient	50.0
	Polyvinylpyrrolidone	150.0
10	Polyethylene glycol	50.0
	Polysorbate 80	10.0
	Magnesium Stearate Ph Eur	2.5
	Croscarmellose Sodium	25.0
	Colloidal Silicon Dioxide	2.5
15	Microcrystalline Cellulose USNF	210.0

20           The polyvinylpyrrolidone, polyethylene glycol, and polysorbate 80 were dissolved in water. The resultant solution was used to granulate the active ingredient. After drying, the granules were screened then extruded at elevated temperatures and pressures. The extrudate was milled and/or  
25           screened, then was blended with the microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The resultant mix was compressed into tablets.

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2.	mg/tablet
Active Ingredient	50.0
Polysorbate 80	3.0
Lactose Ph Eur	178.0
Starch BP	45.0
Pregelatinized Maize Starch BP	22.5
Magnesium Stearate BP	1.5

The active ingredient was sieved and blended with the lactose, starch, and pregelatinized maize starch. The polysorbate 80 was dissolved in purified water. Suitable volumes of the polysorbate 80 solution were added and the powders were granulated. After drying, the granules were screened and blended with the magnesium stearate. The granules were then compressed into tablets.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to the other excipients.

#### FILM COATED TABLETS

The aforementioned tablet formulations were film coated.

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Coating Suspension	% w/w
Opadry white †	13.2
Purified water Ph Eur	to 100.0*

5

\* The water did not appear in the final product. The maximum theoretical weight of solids applied during coating was 20 mg/tablet.

10

† Opadry white is a proprietary material obtainable from Colorcon Limited, UK, which contains hydroxypropyl methylcellulose, titanium dioxide, and triacetin.

15

The tablets were film coated using the coating suspension in conventional film coating equipment.

20

#### CAPSULES

1.	mg/capsule
Active Ingredient	50.0
Lactose	148.5
Polyvinylpyrrolidone	100.0
Magnesium Stearate	1.5

25

30

The active ingredient was sieved and blended with the excipients. The mix was filled into size No. 1 hard gelatin capsules using suitable equipment.

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	2.	mg/capsule
	Active Ingredient	50.0
	Microcrystalline Cellulose	233.5
5	Sodium Lauryl Sulfate	3.0
	Crospovidone	12.0
	Magnesium Stearate	1.5

10                   The active ingredient was sieved and blended with the excipients. The mix was filled into size No. 1 hard gelatin capsules using suitable equipment.

15                   Other doses can be prepared by altering the ratio of active ingredient to excipient, the fill weight, and, if necessary, changing the capsule size.

	3.	mg/capsule
20	Active Ingredient	50.0
	Labrafil M1944CS	to 1.0 ml

25                   The active ingredient was sieved and blended with the Labrafil. The suspension was filled into soft gelatin capsules using appropriate equipment.

#### Inhibitory Effect on cGMP-PDE

30                   cGMP-PDE activity of compounds of the present invention was measured using a one-step assay adapted from Wells et al., *Biochim. Biophys.*

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Acta, 384, 430 (1975). The reaction medium contained 50 mM Tris-HCl, pH 7.5, 5 mM magnesium acetate, 250  $\mu$ g/ml 5'-Nucleotidase, 1 mM EGTA, and 0.15  $\mu$ M 8-[H<sup>3</sup>]-cGMP. The enzyme used was a human recombinant PDE5 (ICOS Corp., Bothell, Washington).

Compounds of the invention were dissolved in DMSO finally present at 2% in the assay. The incubation time was 30 minutes during which the total substrate conversion did not exceed 30%.

The IC<sub>50</sub> values for the compounds examined were determined from concentration-response curves typically using concentrations ranging from 10 nM to 10  $\mu$ M. Tests against other PDE enzymes using standard methodology also showed that compounds of the invention are highly selective for the cGMP-specific PDE enzyme.

#### cGMP Level Measurements

Rat aortic smooth muscle cells (RSMC), prepared according to Chamley et al., *Cell Tissue Res.*, 177, 503-522 (1977), were used between the 10th and 25th passage at confluence in 24-well culture dishes. Culture media was aspirated and replaced with PBS (0.5 ml) containing the compound tested at the appropriate concentration. After 30 minutes at 37°C, particulates guanylate cyclase was stimulated by addition of ANF (100 nM) for 10 minutes. At the end of incubation, the medium was withdrawn, and two extractions were performed by addition of 65% ethanol (0.25 ml). The two ethanolic extracts were pooled and evaporated until dryness, using a Speed-vac system. cGMP was measured



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after acetylation by scintillation proximity immuno-  
assay (AMERSHAM). The  $EC_{50}$  values are expressed as  
the dose-giving half of the stimulation at saturat-  
ing concentrations.

5

### Biological Data

The compounds according to the present  
invention were typically found to exhibit an  $IC_{50}$   
10 value of less than 500 nM and an  $EC_{50}$  value of less  
than 5  $\mu$ M. *In vitro* test data for representative  
compounds of the invention is given in the following  
table:

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Table 1: <i>In vitro</i> Results		
Example No.	IC <sub>50</sub> (nM)	EC <sub>50</sub> (μM)
12	10	0.15
36	<10	0.5
52	20	0.8
63	30	0.35
78	2	0.2
79	<10	0.15
82	20	0.5
84	10	0.4
89	10	<0.1
95	2	0.2
101	10	0.3
115	<10	0.4
117	2	0.2
120	15	0.6
121	20	<1
122	30	<1
123	8	<1
124	8	<1

The hypotensive effects of compounds according to the invention as identified in Table 2 were studied in conscious spontaneously hypertensive rats (SHRs). The compounds were administered orally at a dose of 5 mg/kg in a mixture of 5% DMF and 95% olive oil. Blood pressure was measured from a catheter inserted in the carotid artery and recorded for five hours after administration. The results

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are expressed as Area Under the Curve (AUC) from 0 to 5 hours, mm Hg•hours of the fall in blood pressure over time.

5

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15

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Table 2. <i>In vivo</i> results	
Example No.	SHR AUC PO (mm Hg.h)
36	99
63	95
79	171
82	111
84	77
89	117
95	135
101	136
120	137
121	93
122	108
123	101
124	89

Obviously, many modifications and variations of the invention as hereinbefore set forth can be made without departing from the spirit and scope thereof, and, therefore, only such limitations should be imposed as are indicated by the appended claims.

25

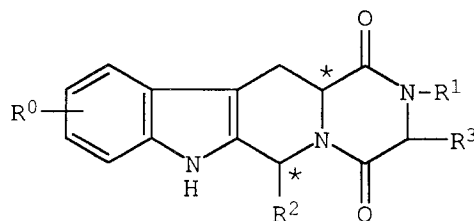
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## WHAT IS CLAIMED IS:

1. A combination comprising:

(a) a compound represented by a formula

(I)



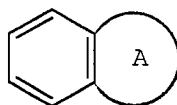
(I)

and salts and solvates thereof, in which:

R<sup>0</sup> represents hydrogen, halogen or C<sub>1-6</sub>-alkyl;

R<sup>1</sup> represents hydrogen, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>-alkenyl, C<sub>2-6</sub>alkynyl, haloC<sub>1-6</sub>alkyl, C<sub>3-8</sub>cycloalkyl, C<sub>3-8</sub>cycloalkylC<sub>1-3</sub>alkyl, arylC<sub>1-3</sub>alkyl, or heteroaryl-C<sub>1-3</sub>alkyl;

R<sup>2</sup> represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan, and pyridine or an optionally substituted bicyclic ring



attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring

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A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen; and

R<sup>3</sup> represents hydrogen or C<sub>1-3</sub>alkyl, or R<sup>1</sup> and R<sup>3</sup> together represent a 3- or 4- membered alkyl or alkenyl chain; and

(b) a second therapeutically active agent,

for simultaneous, separate, or sequential use in the treatment of condition where inhibition of a cGMP-specific PDE is of a therapeutic benefit.

2. A pharmaceutical formulation comprising a combination according to claim 1, together with a pharmaceutically acceptable diluent or carrier.

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3. The combination of claim 1 wherein the condition is stable angina, unstable angina, variant angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, malignant hypertension, pheochromocytoma, congestive heart failure, acute respiratory distress syndrome, acute renal failure, chronic renal failure, atherosclerosis, a condition of reduced blood vessel patency, postpercutaneous transluminal coronary angioplasty, carotid angioplasty, myocardial infarction, post-bypass surgery graft stenosis, a peripheral vascular disease, a vascular disorder, Raynaud's disease, thrombocythemia, an inflammatory disease, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, peptic ulcer, osteoporosis, preterm labor, benign prostatic hypertrophy, a gut motility disorder, or irritable bowel syndrome.

4. The combination of claim 1 wherein the condition is erectile dysfunction in a male or female animal.

5. The combination of claim 1 wherein the second therapeutically active agent comprises a vasodilator, prostaglandin E<sub>1</sub>, prostacyclin, an  $\alpha$ -adrenergic blocker, a mixed  $\alpha$ , $\beta$ -blocker, an  $\alpha_2$ -adrenergic blocker, an ACE inhibitor, an NEP inhibitor, a centrally acting dopaminergic agent, a vasoactive intestinal peptide, a calcium channel blocker, a thiazide, or a mixture thereof.

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6. The combination of claim 5 wherein the vasodilator is selected from the group consisting of an organic nitrate, an organic nitrite, a thionitrite, a thionitrate, an S-nitrosothiol, a nitrosoprotein, a substituted furoxane, a substituted sydnonimine, a nitrosyl complex compound, nitric oxide, or a mixture thereof.

7. The combination of claim 5 wherein the vasodilator is selected from the group consisting of nitroglycerin, isosorbide dinitrate, pentaerythrityl tetranitrate, isosorbide-5-mononitrate, propatyl nitrate, trolnitrate, nicroandil, mannitol hexanitrate, inositol hexanitrate, N-[3-nitratopivaloyl]-6-cysteine ethyl ester, isoamyl nitrite, S-nitroso-N-acetyl-D,L-penicillamine, 1,2,5-oxadiazole-2-oxide, furazan-N-oxide, molsidomine, mesocarb, an iron nitrosyl compound, sodium nitropruside, nitric oxide, and mixtures thereof.

8. The combination of claim 1 wherein the second therapeutically active compound is selected from the group consisting of prostaglandin E1, prostocyclin, apomorphine, yohimbine, phentolamine, prazosin, carvedilol, and mixtures thereof.

9. A method of treating a condition where inhibition of a cGMP-specific PDE is of therapeutic benefit, in a human or a nonhuman animal body, comprising administering to said body a therapeutically effective amount of a combination of claim 1.

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10. The method of claim 9 wherein the cGMP-specific PDE is PDE5.

11. The method of claim 9 comprising a prophylactic or curative treatment of erectile dysfunction in a male or female animal.

12. The method of claim 1 wherein the male or female animal is a human male or female animal.

13. The method of claim 9 wherein the treatment is an oral treatment.



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14. A method of treating stable angina, unstable angina, variant angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, acute respiratory distress syndrome, malignant hypertension, pheochromocytoma, congestive heart failure, acute renal failure, chronic renal failure, atherosclerosis, a condition of reduced blood vessel patency, a peripheral vascular disease, a vascular disorder, thrombocythemia, an inflammatory disease, myocardial infarction, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, peptic ulcer, a gut motility disorder, postpercutaneous transluminal coronary or carotid angioplasty, post-bypass surgery graft stenosis, osteoporosis, preterm labor, benign prostatic hypertrophy, or irritable bowel syndrome, in a human or nonhuman animal body, said method comprising administering to said body a therapeutically effective amount of a combination of claim 1.

15. The method of claim 14 wherein the combination is administered orally.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/19466

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/4985 A61P9/08 A61P15/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	WO 96 38131 A (GLAXO GROUP LTD.) 5 December 1996 (1996-12-05) page 1, line 3 - line 13 page 4, line 10 - line 35 page 7, line 23 -page 9, line 7 page 11, line 11 - line 28 claims 1,5,15,23-26,33,34	1-13
X,Y	WO 97 03675 A (LABORATOIRE GLAXO WELLCOME S.A.) 6 February 1997 (1997-02-06) cited in the application page 1, line 3 -page 6, line 28 page 12, line 15 -page 17, line 27 claims 1-12	1-13



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

3 December 1999

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10/12/1999

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## INTERNATIONAL SEARCH REPORT

Inter national Application No

PCT/US 99/19466

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	WO 96 27372 A (INTERNATIONAL MEDICAL INNOVATIONS, INC.) 12 September 1996 (1996-09-12) page 1, line 20 -page 8, line 13 claims 1-24 ----	1, 2, 4-13
Y	WO 96 34583 A (BAKER NORTON PHARMACEUTICALS, INC.) 7 November 1996 (1996-11-07) page 1, line 1 -page 13, paragraph 2 examples 4-7 claims 1-34 ----	1, 2, 4-13
Y	DE 42 20 264 A (CASSELLA AG.) 23 December 1993 (1993-12-23) page 5, line 60 -page 6, line 1 page 6, line 64 -page 7, line 20 claims 1-10 ----	1-13
Y	WO 95 29172 A (THERABEL RESEARCH S.A.) 2 November 1995 (1995-11-02) page 1, line 1 -page 2, paragraph 2 page 6, last paragraph -page 7, last paragraph ----	1-13
Y	WO 96 28142 A (VIVUS INCORPORATED) 19 November 1996 (1996-11-19) page 1, line 35 -page 2, line 2 page 6, line 19 -page 7, line 23 claims 1, 12 ----	1, 2, 4-13
Y	WO 95 11683 A (THE UPJOHN COMPANY) 4 May 1995 (1995-05-04) page 2, line 11 - line 12 ----	1, 2, 4-13
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Inte.      onal Application No  
PCT/US 99/19466

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	EP 0 611 248 A (B.M.R.A. CORPORATION B.V.) 17 August 1994 (1994-08-17) claims 1-11 ---	1,2,4-13
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Y	WO 92 11851 A (LARAGH J.H.) 23 July 1992 (1992-07-23) claims 1-13 -----	1,2,4-13

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Information on patent family members

International Application No

PCT/US 99/19466

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